REMARKS

Reconsideration of the application in view of the above amendments and the following remarks is requested.

Claims 1-67 are now in this case. Claims 1, 6, 14, 41,42, and 44have been amended to more precisely define the invention. Claims 68- 73 have been added to more completely describe the invention.

Claim 1 is amended to more clearly indicate that a single segmentation mask is used for images of a feature in all wavelength ranges. Claim 6 is amended to more clearly explain the sequence of steps. Claim 14 is amended to include the criterion for selecting the single segmentation mask from the spectral image of largest area. Support for this change is found in page 30, lines 23-25. Claims 41 and 42 have been amended as suggested by Examiner. Claim 42 has also been amended to change the criterion form 100% sensitivity to melanoma to "a defined sensitivity to melanoma". The 100% sensitivity has been reintroduced in claim 73, dependent on claim 42. Claim 44 has been amended in the same way as claim 14. Claims 68-72 are claims dependent on claim 14 which have been rewritten to include all limitation of their parent claims, which makes them allowable as suggested by Examiner. Claims 74-79 are dependent claims introducing explicitly the linear and non-linear combination of estimated values which is supported by the specification on page 4 line 12.

The office action states in section 3 that Claims 1-3, 11, 12, 14-21, 23-31, 41, 42, 44-50, 53-58, and 67 are rejected under Section 35 U.S.C. 103(a) as being unpatentable over Cabib et al, further in view of Lee et al and Bostick et al.

Applicant states that one of ordinary skill in the art would not apply the teaching of Cabib to the present invention. Cabib is overwhelmingly concerned with the combination of very high resolution spectroscopy and high resolution microscopy to the problem of looking at cells.

Cabib in fact explicitly teaches away from the method of the present invention in the following passage:

Col 3 lines 29-34

"All these types of filter and tunable filter based systems have not been used successfully and extensively over the years in spectral imaging for any application, because of their limitations in spectral resolution, low sensitivity, and lack of easy-to-use and sophisticated software algorithms for interpretation and display of the data."

Applicant states that all examples of application of a combination of imaging and spectroscopy that Applicant can conceive of are to be found among the 7 columns (!) of summary of the invention and other description in Cabib. If any such examples are missing, Examiner is requested to point them out for Applicants education. While the Cabib patent is an outstanding example of a careful Patent Attorney describing of the entire world encompassed by the combination of spectral resolution and imaging applied to tissue, the described preferred embodiments and the allowed claims would be read by one of skill in the art as applying the interferometric spectral resolution techniques to microscope images, which are principally images of fluorescent material. For example, the following described embodiment relating to melanoma relates to a fluorescence study of non human melanoma cells *in vitro*, as contrasted to the present invention of *in vivo* imaging of macroscopic lesions and the method of deciding whether the lesion is melanoma or not.

Cabib Col 45-line 45 col 6 line 38

"EXAMPLE 3

5-AMINOLEVULINIC ACID MEDIATED PHOTODINAMIC THERAPY OF MELANOMA TUMORS:
LIGHT-SENSITIZER INTERACTIONS DETERMINED BY SPECTRACUBE.TM. SPECTRAL IMAGING SYSTEM USING THE SIMILARITY MAPPING ALGORITHM.

Photodinamic therapy (PDT) of malignant melanoma has remained only partially understood [Marcus (1992) Photodynamic Therapy-Basic Principles and Clinical Applications. Edited by Henderson and Dougherty. Marcel Dekker, New York. pp. 219-268]. A strong correlation between the degree of

tumor pigmentation and the degree of regression has been found, with the lighter tumors responding much better than darker tumors [Nelson et al. (1988) J Natl. Cancer Inst., 80, 56-60]. It was concluded [Favilla et al. (1991) Br. J Ophthalmol., 75, 718-721] that pigmented melanoma in humans does not respond satisfactorily to PDT, whereas amelanotic melanoma (such as of the iris) do respond positively. On the other hand, the remarkable effectiveness of 5-aminolevulinic acid (ALA) induced PDT of skin lesions and the results of experimental melanoma PDT mediated by ALA [Malik et al. (1987) Biol. Cell, 60, 33-40] have opened up new possibilities for the development of melanoma PDT. It was shown [Malik and Lugaci (1987) Brit. J. Cancer, 56, 589-595; Malik et al. (1989) J. Photobiol. Photochem. B, 4, 195-205; and, Hanania and Malik (1992) Cancer Lett., 65, 127-131] that protopoiphynin (PP) biosynthesized in leukemic cells from the natural precursor 5-ALA is a highly potent photosensitizer for the destruction of cancer cells even by low light-doses. 5-ALA-PDT has been applied successfully to human patients for the selective eradication of skin tumors, especially basal cell carcinoma, as well as for internal solid tumors [Peng et al. (1992) Int. J. Cancer, 52, 433-443]. Topical 5-ALA application, or its systemic injection, has been shown as highly selective both in demarcating the tumor and in its photodestruction [Kennedy and Pottier (1992) J Photochem. Photobiol. B. ,14, 275-292; and, Peng et al. (1992) Int. J. Cancer, 52, 433-443]. These results are a direct consequence of the markedly elevated PP biosynthesis and accumulation in the fast- dividing transformed-cells in comparison to the surrounding normal tissue. 5- ALA- PDT can be considered a safe and powerful tool in selective tumor treatment and one of the challenges is to develop it for melanoma. It was demonstrated that the stimulation of endo-PP biosynthesis in B16 melanoma cells was markedly enhanced by chemical

inducers of poiphyria in order to facilitate efficient photodynamic cell killing [Malik et al. (1987) Biol. Cell, 60, 33-40].

In the present example revealed are primary photochemical processes and photobiological reactions on single cells accumulating endogenous PP in comparison to treatment with exogenous PP. Spectral image analysis of the PP fluorescence showed multiple pixel changes in one cell; at least 100.times.100 (i.e., 10,000) different spectra were derived from a single cell. By the use of the spectral imaging and similarity mapping algorithm, as shown below, it was possible to locate point spectral changes and intracellular photosensitization targets in a single cell."

Applicant states that one of skill in the art of macroscopic imaging would not wade through the 57 pages of Bostick and hence would not notice the several instances buried in the text.

An analysis of the reference by Lee et al cited by Examiner shows that Lee is exclusively interested in the segmentation of images, and the only values cited are "threshold values needed to segment the lesions and the normal skin." Cited in the first line of the first paragraph of "IV. Step 2: Threshold values" on page 603. Applicant states that such values are not related to the estimated values referred to in the claims such as

> "computes at least one estimated value for each digital image at each spectral band which is a function of a characteristic of the region of interest determined by the segmentation mask"

in the sense of the specification. Independent claims 1, 14, and 44 (as amended) are thus patentable over the combination of Cabib and Lee.

Lee differs from the instant invention in that Lee does not apply the mask generated in one spectral band to the other spectral bands. Lee segments *each* image. Lee notes that, for some images, there is no contrast which can be used to generate the boundary, and that the blue image has the least problems with finding the boundary. There is no teaching that the blue image is generally the largest image of the lesion. There is no teaching that the largest image provides the best

segmentation mask. There is no teaching of using a single segmentation mask for images in all spectral bands. Independent claims 1, 14, and 44 (as amended) are thus patentable over the combination of Cabib and Lee.

In addition, Examiner states "Regarding claim 2, Lee et al further disclose the method of claim 1, further comprising estimating at least one value which is a function of the texture of the region of interest (Page 604, paragraphs 1 and 2; intensity value S). Applicant states that intensity value S refers to the maximum number of pixels of one intensity level of normal skin. A curve such as fig. 4 would result from a uniform lesion with no texture, since the curve just gives the number of pixels with a certain intensity value as a function of intensity. (Note the spread in intensity values from normal skin (peak S), which is presumably without texture, is the same as the spread in intensity of light reflected from the lesion (peak M)). Applicant states that Lee et al say nothing about texture. Claim 2 is thus patentable over the combination of Cabib and Lee, and over claim 1.

In addition, Examiner states "Regarding claim 3, Lee et al further disclose the method of claim 1, further comprising estimating at least one value which is a function of the texture of the region of interest (Page 604, paragraphs 1 and 2; intensity value S). The response above answers this statement.

In addition, Examiner states "Regarding claim 11, Lee et al further disclose the method of claim, wherein the segmenting step comprises generating the segmentation mask from a digital image by: removing digital signals from the digital image which corresponds to hair structure;...." Lee states on p 605 col 1 "however, the algorithm had some difficulties in recognizing thick hairs. Over 60% of the poor category in each run .... was degraded by the presence of thick hairs." Lee notes the problem, but does not provide the solution, as does the specification of the instant invention. Claim 11 is thus allowable over Lee in combination with Cabib.

In addition, Examiner states "Regarding claim 17, Cabib et al further disclose the method of claim 14 , wherein the illuminating step further comprises illuminating the region of interest with light in at least one spectral band which penetrates the papilary dermis and re-emitted therefrom (Col 7 lines 60-64)" These lines from Cabib state "According to still further features in the described

preferred embodiments the collimated light is selected from the group consisting of light transmitted through the sample, light reflected from the sample, light scattered from the sample and light emitted from the sample." There is no statement that the light penetrates, and is re-emitted. One of skill in the art would read this section that the light emitted from the sample is fluorescent light, which is in a different wavelength band from the illumination light.

In addition, Examiner states "Regarding claim 19, Cabib et al further disclose the method of claim 17 , wherein the illuminating step further comprises illuminating the region of interest with light in the near infrared spectral band (Column 8 lines3-7)" These lines state "According to still further features in the described preferred embodiments the light originates from a source selected from the group consisting of laser, white light, filtered light, ultraviolet light and a light having a small wavelength range." Infra red is not mentioned in this section. A computer word search of the Cabib file finds no mention of " ir ", or "infra red".

In addition, Examiner states "Regarding claim 20, Cabib et al further disclose the method of claim 14 , further comprising suppressing specular reflections prior to the digital imaging step. (Column 27 line 67, Column 28 lines 1-8)" These lines state "Fluorescence images are then acquired, one image for each dye, by appropriately rotating two filter wheels, one for selecting the excitation wavelength and another for capturing the emission spectrum, or alternatively, rotating one filter wheel aimed at selecting the excitation wavelength, while capturing the emission spectrum by a triple dichroic filter. Approaches in which tunable filters (no moving pails) are used to control the excitation and/or emission wavelength have also been proposed." Applicant does not understand Examiners statement in the light of the above quote. Perhaps Examiner has erred in the citation. In any case, Applicant finds all instances of the word "reflection" in a computer search of Cabib to have no suggestion of " suppressing"

In addition, Examiner states "Regarding claim 21, Cabib et al further disclose the method of claim 1 , wherein the processor converts the digital signals of each of the digital images into values corrected for the non-uniformities of illumination and of response prior to the segmenting step. (Column 27 lines 22-55; Column 33 lines 9-16)" Applicant states that these two passages correct for unwanted light in the wrong spectral band in the first case, and in the second case the ratio of

fluorescence is used to correct for illumination non-uniformity.

The argument above holds also for claim 21.

Regarding claim 23, the above discussion of the Lee reference holds.

Regarding claim 24, Cabib does not disclose segmentation.

Regarding claim 25, Cabib does not disclose segmentation.

Regarding claim 26-31,41, the above discussion of the Lee reference holds.

Further regarding claim 42, Examiner has stated that weight coefficients for a particular training set selected to maximize specificity subject to the constraints of 100% sensitivity to melanoma is a theoretical concept and thus equivalent to Bostock's 92.4% sensitivity. Applicant states that the *criterion* of 100% sensitivity in the *training set* is not a theoretical concept. It is done routinely in present and past performance of the invention. Examiner has apparently confused the *predicted sensitivity* for an image *outside* of the training set with Bostock's numbers.

Bostock's neural network is fundamentally different from the present invention, as is certified by the enclosed affidavit.

Applicant states that the fact that the 100% sensitivity criterion for *their* system works at all was surprising to the inventors, as there should be no way in theory for normally distributed values to produce high specificity under such a criterion. Claim 42 is thus patentable over its parent claim.

In addition, Examiner states "Regarding claim 53, Cabib et al further disclose the system of claim 44 , wherein the filter means comprises a plurality of interference filters mounted on a wheel for stepping any filter into a position intercepting the light from the light source (Column 27 lines 67; Column 28 lines1-8)" These lines state " Fluorescence images are then acquired, one image for each dye, by appropriately rotating two filter wheels, one for selecting the excitation wavelength and another for capturing the emission spectrum, or alternatively, rotating one filter wheel aimed at selecting the excitation wavelength, while capturing the emission spectrum by a triple dichroic filter." Such devices are used for fluorescence excitation.

In addition, Examiner states "Regarding claim 55, Cabib et al further disclose the system of claim 54 , wherein the set of interference filters includes a filter whose center lies in at least oone

spectral band in the near infra red range whose center lies between about 750 and 1000 nm (Figs. 4 and 5, Column 20 lines 31-62)" Cabib does not say anything about a filter for shining light on the sample within the infra red spectral range. Figs. 4 and 5 show fluorescence spectra. In fact, Applicant is suspicious of the data, since in the above cited passage Column 20 lines 31-62 contains the lines "Since such a camera simply integrates the optical signal over the spectral range (e.g.,400 nm to 760 nm) of the CCD array, the `equivalent` monochrome CCD camera image can be computed from the 3D spectral image data base by integrating along the spectral axis, as follows:" Applicant suggests on the basis of this citation that *all* references to infra red, if any may be found, and the figures (in spectral range above 760 nm), be ignored.

In addition, Examiner states "Regarding claim 34, Shindewolf et al further disclose the system of claim 33..... , Shindewolf et al state "The longest distance between the three color centers in each lesion is an important feature of the classification." Shindewolf et al use data from three different wavelengths, and do not disclose intensity moments for one image.

In addition, Examiner states "Regarding claim 35, Shindewolf et al further disclose the system of claim 14..... blotchiness, Shindewolf et al do not discuss blotchiness nor show the method described in the specification.

Regarding claim 10 and 65, Examiner has introduced Tryggvason et al (U.S. 5,660,982) as prior art. Tryggvason et al deal solely with *in vitro* specimen of cells which are treated with modern techniques to identify sequences of subunits of DNA. It is a far stretch of the imagination to imagine that one of ordinary skill in the art of imaging of skin lesions would think to combine such work with the material of the instant invention.

Claims dependent on claim 14 that Examiner has found conditionally allowable are rewritten as independent claims 68-72.

In summary, Lee et al may be removed from prior art consideration for every claim except the claims dealing with segmentation. All other prior art documents have deficiencies which a person of reasonable skill in the art would recognize. Applicant suggests that a combination of 5 documents should not be used to block a patent for an important advance in an important field, where the applicants "do it all right" and teach everyone else how to do it.

Applicant respectfully requests that Examiner enter the enclosed affidavit and material in further support of the inventiveness and the commercial success of the instant invention.

An additional fee of $ 294 is required for 5 extra independent claims and 11 extra total claims. A fee of $55 is due for a 1 month extension of time. A check for $349 is attached. Any insufficiency or overage may be debited or credited to deposit account 08/2240.

On the basis of the above amendments and remarks, reconsideration of this application and its early allowance is requested.

Respectfully,

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I hereby certify that the following **attached** correspondence comprising:

Response and Amendment (20pp)

Affidavit (2 pp)

Supporting documents (13pp)

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